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ARTICLE

A multistate platform model for time-to-event endpoints in oncology clinical trials

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Abstract

A multistate platform model was developed to describe time-to-event (TTE) endpoints in an oncology trial through the following states: initial, tumor response (TR), progressive disease (PD), overall survival (OS) event (death), censor to the last evaluable tumor assessment (progression-free survival [PFS] censor), and censor to study end (OS censor), using an ordinary differential equation framework. Two types of piecewise functions were used to describe the hazards for different events. Piecewise surge functions were used for events that require tumor assessments at the scheduled study visit times (TR, PD, and PFS censor). Piecewise constant functions were used to describe hazards for events that occur evenly throughout the study (OS event and OS censor). The multistate TTE model was applied to describe TTE endpoints from a published phase III study. The piecewise surge functions well-described the observed surges of hazards/events for TR, PD, PFS, and OS occurring near scheduled tumor assessments and showed good agreement with all Kaplan-Meier curves. With the flexibility of piecewise hazard functions, the model was able to evaluate covariate effects in a time-variant fashion to better understand the temporal patterns of disease prognosis through different disease states. This model can be applied to advance the field of oncology trial design and optimization by: (1) enabling robust estimations of baseline hazards and covariate effects for multiple TTE endpoints, (2) providing a platform model for understanding the composition and correlations between different TTE endpoints, and (3) facilitating oncology trial design optimization through clinical trial simulations.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In time-to-event (TTE) analysis, nonparametric Kaplan–Meier curve and semiparametric Cox regression are commonly applied to evaluate endpoints for oncology trials. The underlying baseline hazard received little attention, and the TTE endpoints were not evaluated in an integrated fashion.

WHAT QUESTION DID THIS STUDY ADDRESS?

The developed platform model captures the underlying hazards with better resolution of transitions across different states and allows covariate evaluation in a time-variant fashion, enabling robust estimation of multiple TTE endpoints and covariate effect.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The multistate platform model could serve as a powerful tool to make parametric statistical inferences for multiple TTE endpoints and provide all-inclusive information to support go no-go decision in oncology drug development.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This model can be applied to advance the field of oncology trial design and optimization by providing a more nuanced understanding of drug efficacy and comparisons of diverse treatments regimens/drugs and facilitating oncology trial design optimization through clinical trial simulations.

INTRODUCTION

Various parametric models have been developed to describe time-to-event (TTE) endpoints in oncology trials. Typically, these models assume the event times follow a statistical distribution, that is, exponential or Weibull distribution, and the survival probability and hazard for the event over time can be modeled. Impact of covariate effects on model parameters were mainly evaluated by two approaches. An accelerated failure time model evaluates covariate effects on the event time, and a proportional hazards model evaluates covariates that act on the hazard of the events.[1] Due to the limited selection of statistical distributions, models which require an assumption of a distribution for event times, have challenges in capturing the survival probability when the event times do not follow any typical statistical distributions, resulting in less-than-optimal model fit and potential bias in parameter estimation. Another type of parametric model, the piecewise hazard model, has been evaluated by Holford and Friedman.[2,3] The model describes the baseline hazards in a piecewise constant manner and provides greater flexibility for describing survival probability curves of various shapes. Whereas distribution assumptions are required for parametric TTE models, nonparametric and semiparametric methods make no assumptions about the distribution of event times and no estimation of the underlying baseline hazard for the event is needed. Hence, nonparametric Kaplan–Meier (KM) curves and semiparametric Cox regression are used extensively to evaluate TTE data. Hence, the underlying baseline hazard receives little attention and is rarely reported in literature. Lack of information on baseline hazard makes it challenging to conduct clinical trial simulations for future trials, explore different clinical trial designs, and inform drug development in oncology trials.

Despite the ultimate goal of oncology treatments to extend overall survival (OS), it is important to have surrogate endpoints to determine effectiveness of treatment early in the trial and speed up drug development and bring efficacious and innovative medicines to patients quickly. Response evaluation criteria in solid tumors (RECIST) criteria was developed to use tumor response (TR) and time to development of progressive disease (PD) as important early endpoints in oncology clinical trials.[4] Although the agents achieving better TR and delayed times to PD are expected to improve OS, the relationships between these early endpoints and OS are not always confirmed. Quantitative multistate models to jointly describe early and late TTE endpoints, such as time-to-response (TTR), time to progressive disease (TTP), progression-free survival (PFS), and OS, would be valuable to better understand the relationships between these endpoints and see how patients respond to treatment through states of disease prognosis. Few multistate models with "initial," "progression," and "death" states were proposed to evaluate PFS and OS jointly.[5–8] These models were able to quantify the interdependence between PFS and OS, to explore confounding effects that might explain the possible discrepancies in OS and PFS, and to distinguish TTP and post-progression survival from PFS and OS. Krishnan et al. expanded the multistate model to incorporate drug exposure and tumor growth inhibition models and provide a better understanding of drug efficacy and characterization of different states.[9] The model allowed researchers to jointly estimate transition rates based on subjects' pharmacokinetics, TR, and TTE data; and to investigate predictors for different TTE endpoints. Nevertheless, these parametric multistate

models implemented typical statistical distributions to describe the event times, and these models may have challenges describing the survival probability compared to a KM curve. To overcome these limitations, the aims of the current analysis were to (1) develop a flexible parametric model to better describe the temporal patterns of disease prognosis through different states, (2) apply the developed model to estimate survival probabilities and hazards for all key TTE endpoints from a phase III oncology trial, and (3) conduct evaluations of covariate effects under the parametric multistate model framework.

METHODS

Multistate model

The multistate model was developed to describe the following states: initial state (state 1), state of TR (state 2), state of PD (state 3), state of the tumor assessment censor (PFS censor, state 4), state of OS event (state 5), and state of OS censor (state 6) using an ordinary differential equation (ODE) framework. All subjects started from initial state in the model after randomization. The subject in the initial state could either transit to state of TR, PD, PFS censor, OS event, or OS censor from the initial state. If the subject had TR, the subject then could transit to state of PD, PFS censor, OS, or OS censor from the state of TR and so on. All subjects would be in one of the states at any time in the trial. The transition rates between states can be considered as hazards of the transitions. The multistate model is shown as a simplified model schematic for illustration purposes (Figure 1a), or a complete model schematic to include all states and transitions (Figure 1b).

The model is expressed as the following ODEs:

$$dA_1(t)/dt = -\left(H_{1\_2}(t)+H_{1\_3}(t)+H_{1\_4}(t)+H_{1\_5}(t)+H_{1\_6}(t)\right)\cdot A_1(t) \quad (1)$$

$$dA_{1\_2}(t)/dt = H_{1\_2}(t)\cdot A_1(t) - \left(H_{12\_3}(t)+H_{12\_4}(t)+H_{12\_5}(t)+H_{12\_6}(t)\right)\cdot A_{1\_2}(t) \quad (2)$$

$$dA_{1\_3}(t)/dt = H_{1\_3}(t)\cdot A_1(t) - \left(H_{13\_5}(t)+H_{13\_6}(t)\right)\cdot A_{1\_3}(t) \quad (3)$$

$$dA_{1\_4}(t)/dt = H_{1\_4}(t)\cdot A_1(t) - \left(H_{14\_5}(t)+H_{14\_6}(t)\right)\cdot A_{1\_4}(t) \quad (4)$$

$$dA_{1\_5}(t)/dt = H_{1\_5}(t)\cdot A_1(t) \quad (5)$$

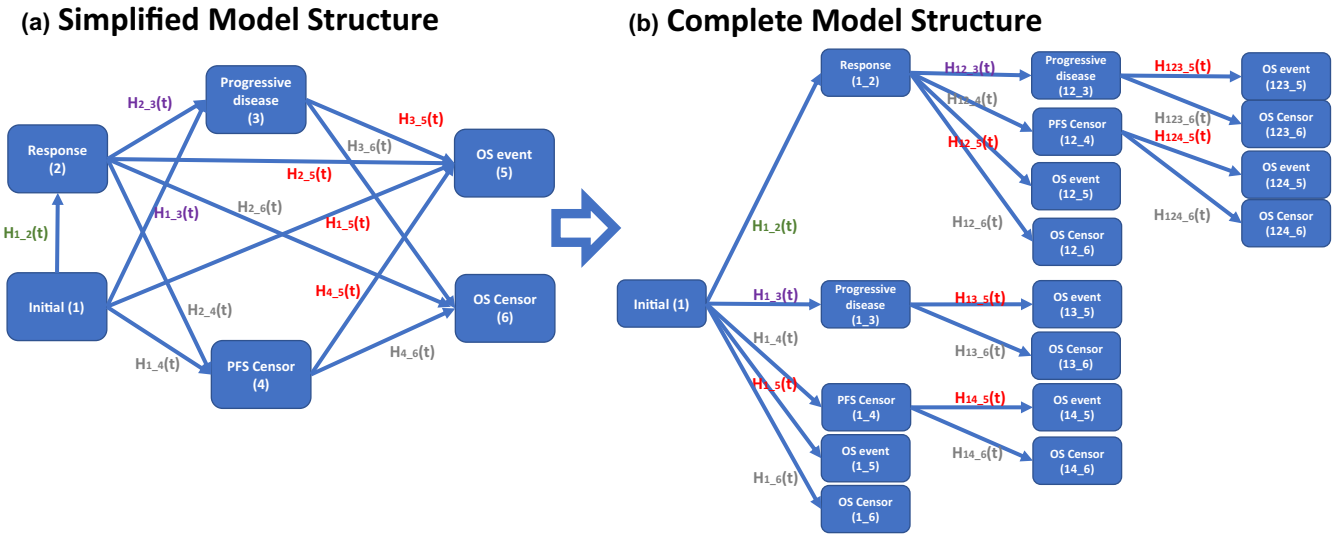

FIGURE 1 Model schematics: (a) Simplified model structure, (b) Complete model structure. The multistate model was developed to describe the transitions through following states: initial state (state 1), state of TR (state 2), state of PD (state 3), state of the tumor assessment censor (PFS censor; state 4), state of OS event (state 5), and state of OS censor (state 6). All subjects started from initial state. After randomization, they can transit from initial state to other states. $H_S(t)$ represents hazard toward state S at time t. As the history of early transitions could affect the later hazards, the information of early transitions is kept in the notations. For example, hazard function $H_{123\_5}(t)$ represents the hazard of transition from the state of PD (state 3) to state of OS event (state 5) for subjects who previously transited from the initial state (state 1) to state of TR (state 2) and then to state of PD (state 3). The hazard functions in blue represents the hazard to TR, the hazard functions in purple represent the hazards to progressive disease, hazard functions in red represent the hazards to OS event (death), and hazard functions in gray represent the hazards to PFS censor and OS censor. OS, overall survival; PD, progressive disease; PFS, progression-free survival; TR, tumor response.

$$dA_{1\_6}(t)/dt = H_{1\_6}(t) \cdot A_1(t) \quad (6)$$

$$dA_{12\_3}(t)/dt = H_{12\_3}(t) \cdot A_{1\_2}(t) - \left(H_{123\_5}(t) + H_{123\_6}(t)\right) \cdot A_{12\_3}(t) \quad (7)$$

$$dA_{12\_4}(t)/dt = H_{12\_4}(t) \cdot A_{1\_2}(t) - \left(H_{124\_5}(t) + H_{124\_6}(t)\right) \cdot A_{12\_4}(t) \quad (8)$$

$$dA_{12\_5}(t)/dt = H_{12\_5}(t) \cdot A_{1\_2}(t) \quad (9)$$

$$dA_{12\_6}(t)/dt = H_{12\_6}(t) \cdot A_{1\_2}(t) \quad (10)$$

$$dA_{13\_5}(t)/dt = H_{13\_5}(t) \cdot A_{1\_3}(t) \quad (11)$$

$$dA_{13\_6}(t)/dt = H_{13\_6}(t) \cdot A_{1\_3}(t) \quad (12)$$

$$dA_{14\_5}(t)/dt = H_{14\_5}(t) \cdot A_{1\_4}(t) \quad (13)$$

$$dA_{14\_6}(t)/dt = H_{14\_6}(t) \cdot A_{1\_4}(t) \quad (14)$$

$$dA_{123\_5}(t)/dt = H_{123\_5}(t) \cdot A_{12\_3}(t) \quad (15)$$

$$dA_{123\_6}(t)/dt = H_{123\_6}(t) \cdot A_{12\_3}(t) \quad (16)$$

$$dA_{124\_5}(t)/dt = H_{124\_5}(t) \cdot A_{12\_4}(t) \quad (17)$$

$$dA_{124\_6}(t)/dt = H_{124\_6}(t) \cdot A_{12\_4}(t) \quad (18)$$

$A_S(t)$ represents the expected number of subjects in state S at time t at risk of transition to other states as described in Figure 1b. For example, $A_{12\_3}(t)$ represents the expected number of subjects at risk in the state of PD (state 3) for those who previously transited from the initial state (state 1) to TR (state 2) and then to PD (state 3). $H_S(t)$ represents hazard toward state S at time t. As the history of early transitions could affect the later hazards, the information of early transitions is kept in the notations. For example, hazard function $H_{123\_5}(t)$ represents the hazard from PD (state 3) to OS event (state 5) for subjects who previously transited from the initial state (state 1) to TR (state 2) and then to PD (state 3). $H_{123\_5}(t)$ would be different from $H_{13\_5}(t)$. Although both the hazard functions are referring to the transition from PD (state 3) to OS event (state 5), $H_{123\_5}(t)$ refers to the transition for subjects who previously had transited from initial (state 1) to TR (state 2), whereas $H_{13\_5}(t)$ applies to subjects who transition from state 1 to state 3 to state 5 without TR. All subjects are in the initial state at time 0. The initial conditions are set as follows:

$$A_1(0) = \text{total number of subjects} \quad (19)$$

$$A_{1\_2}(0) = A_{1\_3}(0) = \ \ldots \ = A_{124\_6}(0) = 0 \quad (20)$$

According to the definition of hazard, $H(t) = -(dS(t)/dt)/S(t)$, and only accounting for subjects who are at risk of the events (e.g., excluding subjects in other states having no risk of the events), the survival probabilities for OS, OS censor, PFS, PFS censor, ($S_{OS}, S_{OS\_C}, S_{PFS}$, and S_{PFS_C}) and cumulative probability for PD and TR (F_{TTP} and F_{TTR}) can be derived from hazard functions and expected number of subjects in different states as described by Nagase *et al.* as follows.[8]

$$H_{OS}(t) = \frac{H_{1\_5}(t) \cdot A_1(t) + H_{12\_5}(t) \cdot A_{1\_2}(t) + H_{13\_5}(t) \cdot A_{1\_3}(t) + H_{14\_5}(t) \cdot A_{1\_4}(t) + H_{123\_5}(t) \cdot A_{12\_3}(t) + H_{124\_5}(t) \cdot A_{12\_4}(t)}{A_1(t) + A_{1\_2}(t) + A_{1\_3}(t) + A_{1\_4}(t) + A_{12\_3}(t) + A_{12\_4}(t)} \quad (21)$$

$$H_{OS\_C}(t) = \frac{H_{1\_6}(t) \cdot A_1(t) + H_{12\_6}(t) \cdot A_{1\_2}(t) + H_{13\_6}(t) \cdot A_{1\_3}(t) + H_{14\_6}(t) \cdot A_{1\_4}(t) + H_{123\_6}(t) \cdot A_{12\_3}(t) + H_{124\_6}(t) \cdot A_{12\_4}(t)}{A_1(t) + A_{1\_2}(t) + A_{1\_3}(t) + A_{1\_4}(t) + A_{12\_3}(t) + A_{12\_4}(t)} \quad (22)$$

$$H_{PFS}(t) = \frac{H_{1\_3}(t) \cdot A_1(t) + H_{1\_5}(t) \cdot A_1(t) + H_{12\_3}(t) \cdot A_{1\_2}(t) + H_{12\_5}(t) \cdot A_{1\_2}(t)}{A_1(t) + A_{1\_2}(t)} \quad (23)$$

$$H_{PFS\_C}(t) = \frac{H_{1\_4}(t) \cdot A_1(t) + H_{1\_6}(t) \cdot A_1(t) + H_{12\_4}(t) \cdot A_{1\_2}(t) + H_{12\_6}(t) \cdot A_{1\_2}(t)}{A_{1(t)} + A_{1\_2}(t)} \quad (24)$$

$$H_{TTP}(t) = \frac{H_{1\_3}(t) \cdot A_1(t) + H_{12\_3}(t) \cdot A_{1\_2}(t)}{A_1(t) + A_{1\_2}(t)} \quad (25)$$

$$H_{TTR}(t) = H_{1\_2}(t) \quad (26)$$

$$S_{OS}(t) = \exp\left[-\int_0^t H_{OS}(u)du\right] \quad (27)$$

$$S_{OS\_C}(t) = \exp\left[-\int_0^t H_{OS\_C}(u)du\right] \quad (28)$$

$$S_{\mathrm{PFS}}(t) = \exp\left[-\int_0^t H_{\mathrm{PFS}}(u)\mathrm{d}u\right] \quad (29)$$

$$S_{\mathrm{PFS\_C}}(t) = \exp\left[-\int_0^t H_{\mathrm{PFS\_C}}(u)\mathrm{d}u\right] \quad (30)$$

$$F_{\mathrm{TTP}}(t) = 1 - \exp\left[-\int_0^t H_{\mathrm{TTP}}(u)\mathrm{d}u\right] \quad (31)$$

$$F_{\mathrm{TTR}}(t) = 1 - \exp\left[-\int_0^t H_{\mathrm{TTR}}(u)\mathrm{d}u\right] \quad (32)$$

By combining the individual hazards and expected numbers of subject at risk at different states, the multistate model could be used to estimate clinically meaningful endpoints, such as TTR, TTP, PFS, and OS as well as censoring events to PFS and OS jointly.

Piecewise hazard functions

Time-variant piecewise functions were used to describe hazards across states over time in the multistate model. Two types of piecewise functions were implemented. Events that require tumor assessments by computed tomography/magnetic resonance imaging scans (CT/MRI) in clinics or hospitals, including TR, PD, and PFS censoring events, occur exclusively at the study visit. Therefore, surge functions were used to describe these transitions occurring mainly at study visit times.[10] Constant piecewise functions were used to describe transitions that occur randomly over time. Given a series of cutoff timepoints $0 = T_1 < T_2 < \ldots < T_k < \ldots < T_m$ post randomization, the hazard function corresponding to time, t, in the k-th time segment can be expressed as follows.

$$H_{\mathrm{surge},k}(t) = \begin{cases} \dfrac{\theta_{\mathrm{surge},k}}{\left(\frac{t-T_{\mathrm{visit},k}}{w}\right)^4 + 1}, & \text{if } T_k \le t < T_{k+1} \\ 0, & \text{otherwise} \end{cases} \quad (33)$$

$$H_{\mathrm{constant},k}(t) = \begin{cases} \theta_{\mathrm{constant},\ k}, & \text{if } T_k \le t < T_{k+1} \\ 0, & \text{otherwise} \end{cases} \quad (34)$$

For the surge function $H_{\mathrm{surge},k}(t)$, $\theta_{\mathrm{surge},k}$ represents the surge amplitude, w represents the width of the surge, and $T_{\mathrm{visit},k}$ represents for the study visit time that occurs within the k-th time segment from T_k to T_{k+1}. For constant hazard function $H_{\mathrm{constant},k}(t)$, $\theta_{\mathrm{constant},\ k}$ represents the constant hazard for the k-th time segment from T_k to T_{k+1}. The length of the time segments could be set to be equal to the length of the intervals of the scheduled study visits, for example, 6 weeks. The starting time and end time of the time segment would be half of the time interval before and after the study visit time, respectively, for example, 3 weeks before and after the study visit time. In this way, the time of the surge would be assumed to occur at the designated study visit times per study protocol and does not need to be estimated. For time segments with no events, the hazards for the corresponding time segments were fixed to zero according to the observed data. This avoids unnecessary parameter estimation and prevents numerical difficulties. Based on the observed trial data and clinical study protocol, the length of time segments and use of surge or constant piecewise function could be adjusted accordingly.

Likelihood calculation

Assuming the hazards/survival probabilities for the competing transition events are independent, the likelihoods of transitions can be calculated based on the observed transitions, transition times, survival probability functions, and the hazard functions. For example, considering the transition times from the initial state (state 1) to other states (states 2–6) are random variables with probability density functions of $f_{1\_2}(t)$, $f_{1\_3}(t)$, $f_{1\_4}(t)$, $f_{1\_5}(t)$, and $f_{1\_6}(t)$, all transitions are competing events leaving state 1, and only one of the competing events, for example, state 1–state 5, can be observed at time t and the rest of the unobservable event times would occur after time t. The likelihood for the transition event can be calculated as follows:

$$\begin{aligned} S_{1\_2}(t)\cdot S_{1\_3}(t)\cdot S_{1\_4}(t)\cdot S_{1\_6}(t)\cdot f_{1\_5}(t) = S_{1\_2}(t)\cdot S_{1\_3}(t) \\ \cdot S_{1\_4}(t)\cdot S_{1\_5}(t)\cdot S_{1\_6}(t)\cdot H_{1\_5}(t) \end{aligned} \quad (35)$$

$S_{i\_j}(t)$ represents the survival probability of the transition event from i to j. $H_{i\_j}(t)$ represent the hazard of transition from i to j at time t. Because $f_{1\_5}(t)$ can be expressed as $S_{1\_5}(t)\cdot H_{1\_5}(t)$, the likelihood could be expressed conveniently as the product of survival probabilities of no transition from state 1 to states 2 to 6 at time t and the hazard for transiting from state 1 to state 5 at time t. Parameters can be estimated based on the likelihoods of all observed transitions. The likelihood calculation is based on the observed states and also previous states. The likelihoods for transitions to censoring events were also calculated.

Evaluation of covariate effects

The covariate effect can be evaluated based on the following two approaches. The first one assumes hazard

ratios at different covariate levels are proportional and remain unchanged over the entire time course as follows:

$$H_i(t|X_i) = H_0(t)\exp(\boldsymbol{\beta^T X_i}) \quad (36)$$

Where $H_i(t|\boldsymbol{X_i})$ is the conditional hazard function given the covariate, $\boldsymbol{X_i}$, from subject i, $\boldsymbol{\beta^T}$ is a vector of regression coefficients, and $H_0(t)$ represents the underlying baseline piecewise hazard function. In contrast to the semiparametric Cox regression model that the nuisance underlying baseline hazard is not estimated, $H_0(t)$ in parametric multistate model was estimated together with $\boldsymbol{\beta^T}$.

The second one assumes the hazards at different covariate levels are proportional within a time segment, but the hazard ratio can be time-variant through the time segments. The flexibility of piecewise hazard functions was utilized in the model. The covariate model is expressed as follows:

$$H_{i,k}(t|X_i) = H_{0,k}(t)\exp(\boldsymbol{\beta_k^T X_{i,k}}) \ , if\ T_k \le t < T_{k+1} \quad (37)$$

Where $H_{i,k}(t|\boldsymbol{X_i})$ is the conditional hazard function given the covariate, $\boldsymbol{X_{i,k}}$, from subject i, $\boldsymbol{\beta_k^T}$ is a vector of regression coefficients, and $H_{0,k}(t)$ represents the underlying baseline piecewise hazard function for the k-th time segment from T_k to T_{k+1}.

Analysis dataset

The multistate model was applied to a clinical dataset from www.projectdatasphere.org, maintained by Project Data Sphere for demonstration purpose using the proposed method.[11] Neither Project Data Sphere nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this analysis. The TTE data were from the phase III trial SQUIRE, which evaluated necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small cell lung cancer.[12] The data used in the analysis included 548 subjects who were randomized to the control group (gemcitabine and cisplatin) in the trial. The dataset was built based on ADaM datasets from Project Datasphere. No subjects were excluded. No missing data were reported. The analysis dataset is provided in the supplementary materials.

Software and parameter estimation

All analyses were conducted using R version 4.2.2 or higher. Model fittings were conducted using cmdstanr package version 0.5.2, post-processing analyses requiring solving ODEs were performed using rxode2 package,[13] and Cox regressions were conducted using the survival package.[14] Posterior distributions of parameters were estimated using No-U-Turn sampler in Stan with at least 1000 sampling iterations from four chains.[15] Non-informative improper priors (e.g., improper uniform priors) were used in the analysis.

RESULTS

Base model development

The base multistate model was developed to describe the TTE data from 548 subjects who were randomized to the control group in the phase III trial SQUIRE. The underlying baseline hazard functions were estimated with the cut-off times of 0, 21, 63, 105, 147, 189, 231, 273, 315, 357, 399, 441, 483, 525, 861, and 1173 days, which were determined based on the study visit times and observed TTE data. The goodness-of-fit figures for survival probabilities for OS, OS censor, PFS, and PFS censor, and cumulative probabilities for PD and TR against the corresponding KM curves are presented in Figure 2. Overall, the parametric piecewise model provides robust fits to data and recapitulates the KM curves. The estimated posterior distributions of parameters are summarized in the supplementary materials.

Composition of events and relationships between the TTE endpoints over time

The composition for the TTE endpoint of interest can be explored to see how the previous states could contribute to the probability of the event of interest over time. For example, the composition of OS events was evaluated as shown in Figure 3a. The figure provides a longitudinal evaluation of probability of OS events for subjects with or without TR and/or PD and how these events contributed to the overall OS events. With the estimated posterior distributions for survival probabilities for different TTE endpoints, the correlations between OS and other TTE endpoints can be evaluated as shown in Figure 3b. OS showed strong to moderate correlation with the subdivided OS for subjects who have no TR or PD for the first 336 days (correlation: >0.5) and moderate correlation with the subdivided OS for subjects who had OS events after PD without TR after 336 days (correlation: 0.3–0.5). OS showed strong to moderate correlation with PFS for the first 336 days (correlation: 0.35–0.75) and weak to moderate correlation with PFS after 336 days (0.2–0.35) for this phase III trial. PFS events include PD events and death events. As most early PFS events were death events for OS, high correlation between PFS and OS was observed initially. The correlation

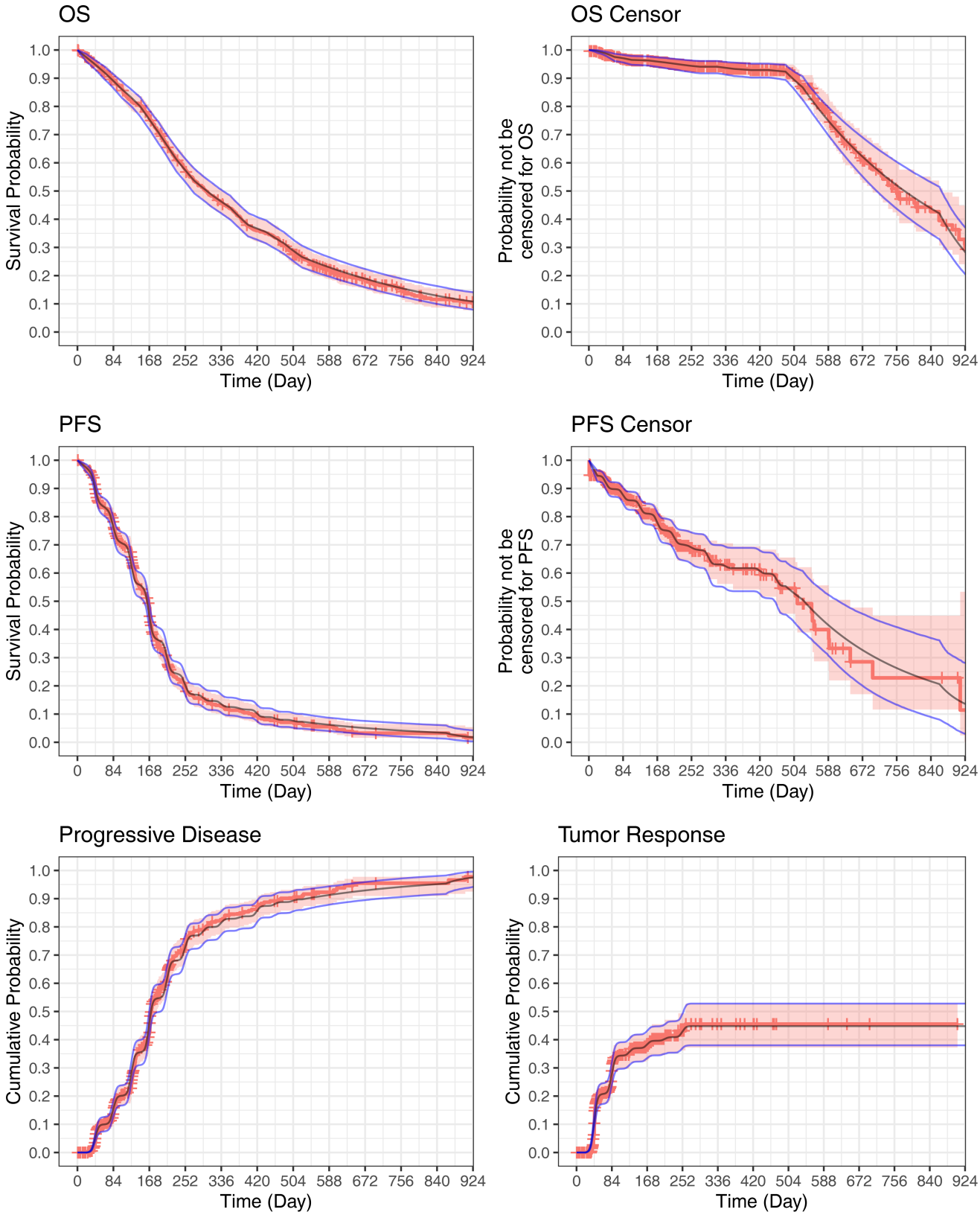

FIGURE 2 Goodness-of-fit plots for estimated survival probabilities for OS, OS censor, PFS, and PFS Censor, and cumulative probabilities for PD and TR against the corresponding KM curves. Black and blue curves represent the estimated probability curves and the corresponding 95% Bayesian credible intervals, respectively, from the multistate platform model. The red curves and bands represent the KM curves and corresponding 95% confidence bands. KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TR, tumor response.

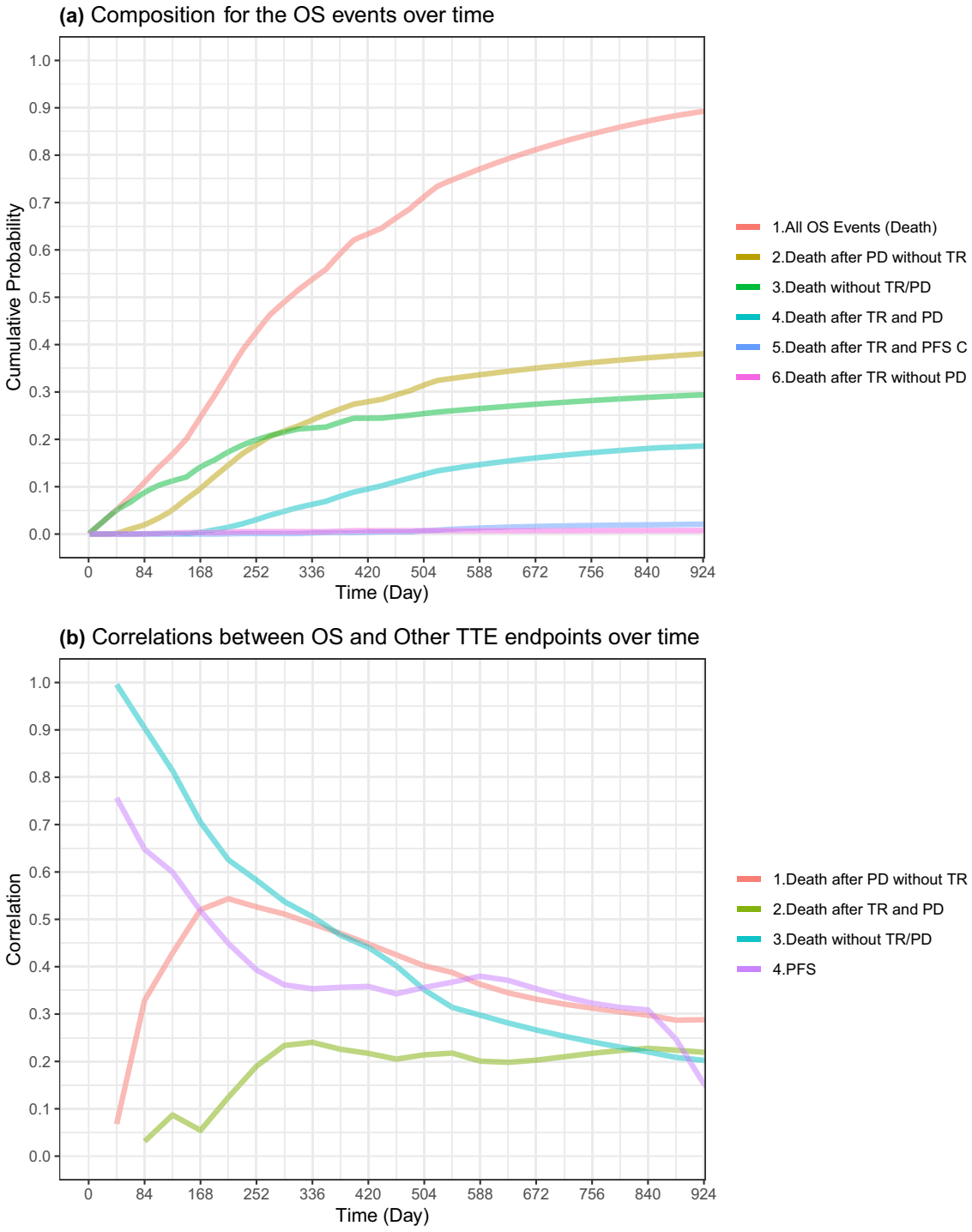

FIGURE 3 (a) Composition for the OS events (deaths) over time and (b) correlations between OS and other TTE endpoints over time. All OS events (death) includes all other mutually exclusive death events: death after PD without TR, death without TR/PD, death after TR and PD, death after TR and PFS censor, and death after TR without PD. OS, overall survival; PD, progressive disease; PFS: progression-free survival; PFS C: censor to progression-free survival; TR, tumor response; TTE, time-to-event.

became lower when the PFS events contained more PD events later in the trial. Let us say the correlation is 0.75 on day 42, this means if someone has a PFS event on day 42, the PFS event is more likely a death event. When a person reaches day 840, the PFS event is likely to be a PD event instead of a death event.

Evaluation of covariate effect

Baseline Eastern Cooperative Oncology Group (ECOG) score was evaluated as a covariate in the multistate model for illustration purpose using the proposed methods. First, the effect of ECOG on hazard/transition rates for

OS, FPS, TTP, or TTR was evaluated assuming proportional hazards over the entire time course. The ratios of $H_{OS}(t)$, $H_{PFS}(t)$, $H_{TTP}(t)$, and $H_{TTR}(t)$ for subjects with high ECOG score (ECOG > 0) and low ECOG score (ECOG = 0) were estimated from the multistate model and compared with the results from semiparametric Cox regression in Table 1. Overall, the estimated hazard ratios from the proposed method are in line with the estimated hazard ratios from Cox regression.

Second, the effects of ECOG on all hazard included in the model through all time segments were evaluated. For the time segment with no events at different covariate levels, the corresponding hazard ratio cannot be estimated and was assumed to be 1 over the time segment. Under the multistate model framework, the hazard ratios for all individual transitions were estimated and presented in Figure 4. The figure demonstrates the ability of the multistate model to break down the covariate effects into different transitions and time segments.

With the estimated covariate effects and underlying baseline hazards, the survival probabilities for OS and PFS, and cumulative probabilities for PD and TR at different covariate levels could be estimated according to Equations 21–32. The goodness-of-fit figures for survival probabilities for OS and PFS, and cumulative probabilities for PD and TR for subjects with low and high baseline ECOG scores against the corresponding KM curves are presented in Figure 5. The parametric multistate model well described the survival and cumulative probabilities for subjects at different covariate levels and recapitulated the KM curves. The estimated hazard ratios for OS, PFS, TTP, and TTR, by assuming (1) proportional ratios over the entire time course and (2) proportional within time segments, are presented in Figure 6. The estimated time-variant hazard ratios could be used to confirm covariate effect and provide better understandings of covariate effects over time.

DISCUSSION

A full parametric multistate model was developed to characterize transitions between key states in an oncology phase III clinical trial. By implementing the piecewise surge and constant functions to describe the hazards for different events, the model could provide robust fits to TTE data, similar to the fits from the estimated KM curves. The model can be implemented to evaluate covariate effects on the hazards for the TTE endpoints and provide comparable analysis results from Cox regressions. In contrast to Cox regression which focuses on estimating hazard ratio whereas the baseline hazards cancel out in the partial likelihood calculation, the proposed model focuses on estimating baseline hazard and then covariate effects on top of the baseline hazard. With the piecewise functions, the model allows the hazards to vary over the time segments, which enables the evaluation of covariate effects on hazards in a time-variant fashion. The proposed multistate platform provides a quantitative approach for better understanding the temporal patterns of disease prognosis through different disease states and summarizes how a covariate (or treatment) could affect disease prognosis in a longitudinal fashion.

Although various parametric methods had been proposed to describe TTE data, few of them were able to provide data fits as good as the estimated KM curves, especially when zigzags in PFS are observed. The proposed parametric piece-wise hazard functions provide satisfactory fits to TTE data and facilitate comparisons of the baseline hazards and survival probabilities across different trials. Moreover, censoring, a key component often ignored from

TABLE 1 Estimated hazard ratios for baseline ECOG effects (ECOG = 0 vs. ECOG > 0) on OS, PFS, TTP, and TTR by the multistate model and Cox regression.

Modeling approach	Endpoints	Estimated hazard ratio	90% CS from Multistate model and 90% CI from Cox regression
Multistate model	OS	1.38	[1.16, 1.65]
	PFS	1.21	[1.02, 1.45]
	TTP	1.10	[0.905, 1.33]
	TTR	0.838	[0.636, 1.10]
Cox regression	OS	1.39	[1.13, 1.70]
	PFS	1.26	[1.02, 1.55]
	TTP	1.14	[0.902, 1.43]
	TTR	0.831	[0.602, 1.15]

Note: Cox regression was conducted in R using survival package.

Abbreviations: CI, confidence interval; CS, Bayesian credible set; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTR, time to response.

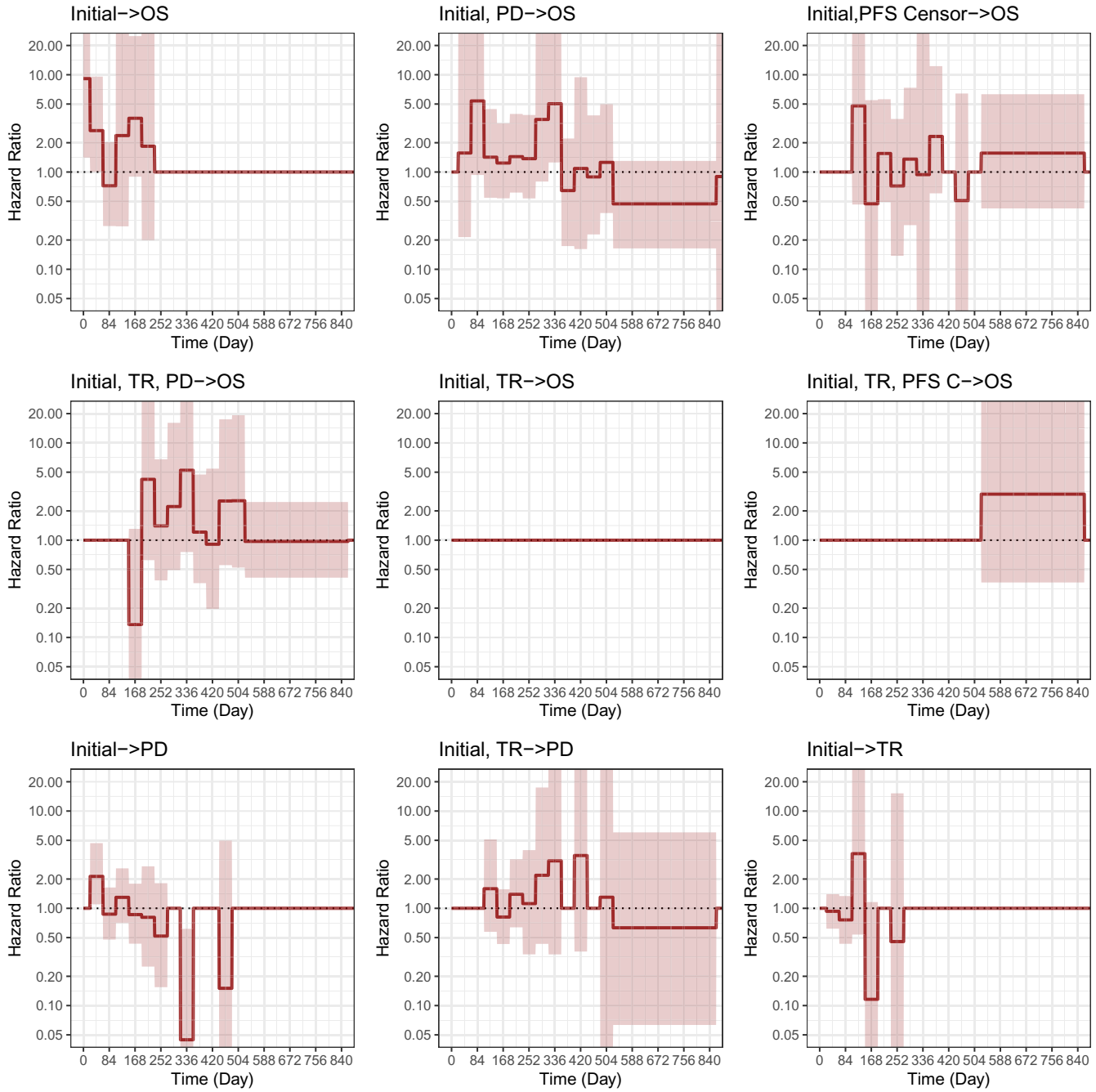

FIGURE 4 Estimated hazard ratios for all transitions included in the multistate model for subjects with high baseline ECOG scores relative (ECOG > 0) to the subjects with low baseline ECOG scores (ECOG = 0). The estimated ratios and the corresponding 95% Bayesian credible bands by assuming proportional ratios only within time segments are shown in red. Low ECOG Score: ECOG = 0; High ECOG Score: ECOG > 0; The limits of *y*-axes were set to 0.05 and 20 for better visualization of the temporal trends. ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PD, progressive disease; PFS Censor, censor to progression-free survival; TR, tumor response.

TTE analysis, is properly described by the multistate approach which enables exploration of censoring mechanism and provides a better understanding on when they occur most and how the history of previous transitions could affect the censoring rate. This would be important for study planning and sample size determination.

It is of interest to understand how the previous transition, for example, TR could affect later event rates such as OS. However, directly comparing survival probabilities for the responders and nonresponders would be inappropriate, and it leads to biased estimates and potential misleading conclusions because the responders must live long enough for response to be observed, which is not required for nonresponders.[16] The proposed multistate model has the history of the previous states incorporated as a part of model structure. The effects of the previous transitions

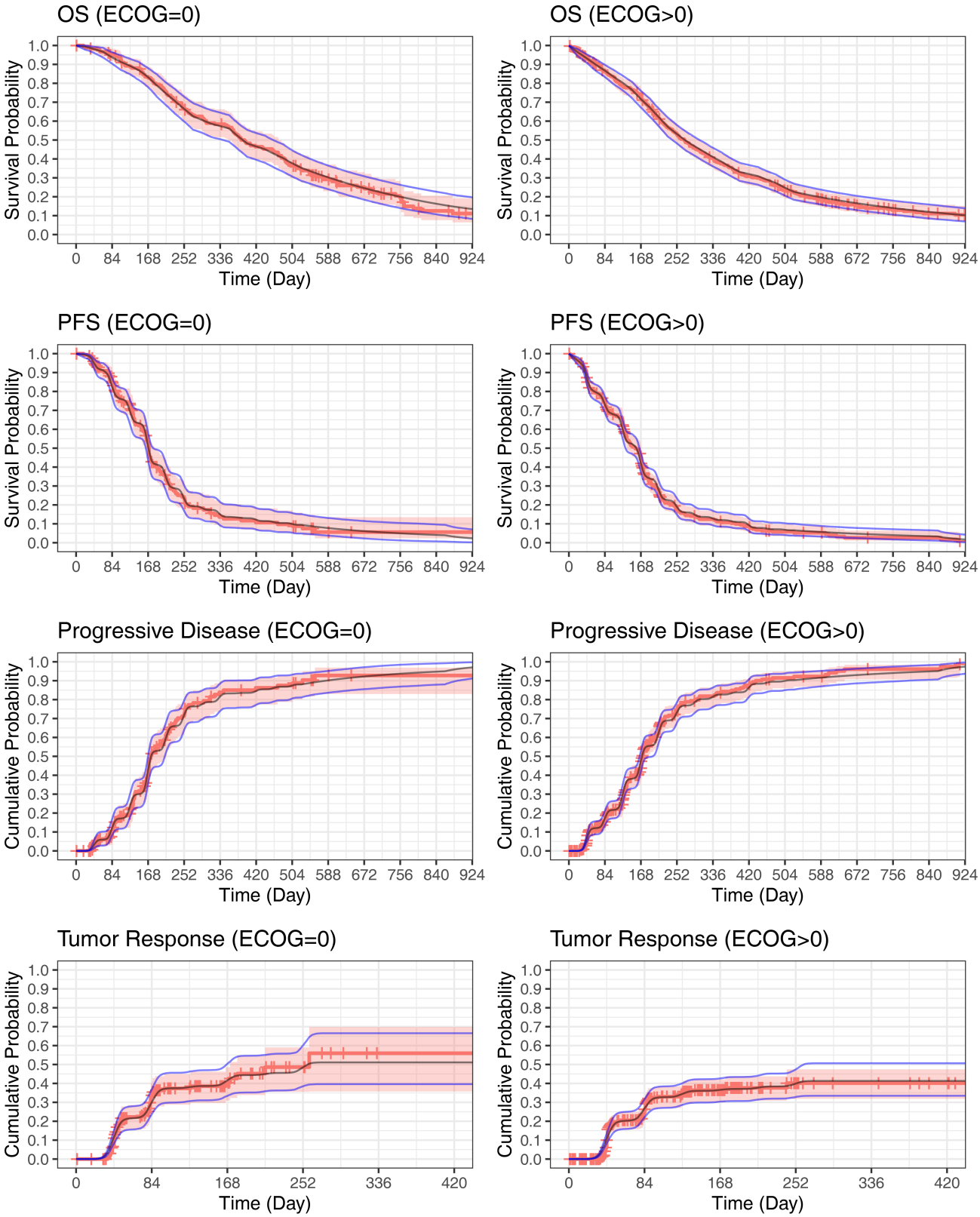

FIGURE 5 Goodness-of-fit plots for survival probabilities for OS, OS censor, PFS, and PFS censor, and cumulative Probabilities for PD and TR for subjects with low and high baseline ECOG scores against the corresponding KM curves. Black and blue curves represent the estimated probability curves and the corresponding 95% Bayesian credible intervals, respectively, from the multistate platform model. The red curves and bands represent the KM curves and corresponding 95% confidence bands. ECOG, Eastern Cooperative Oncology Group; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TR, tumor response.

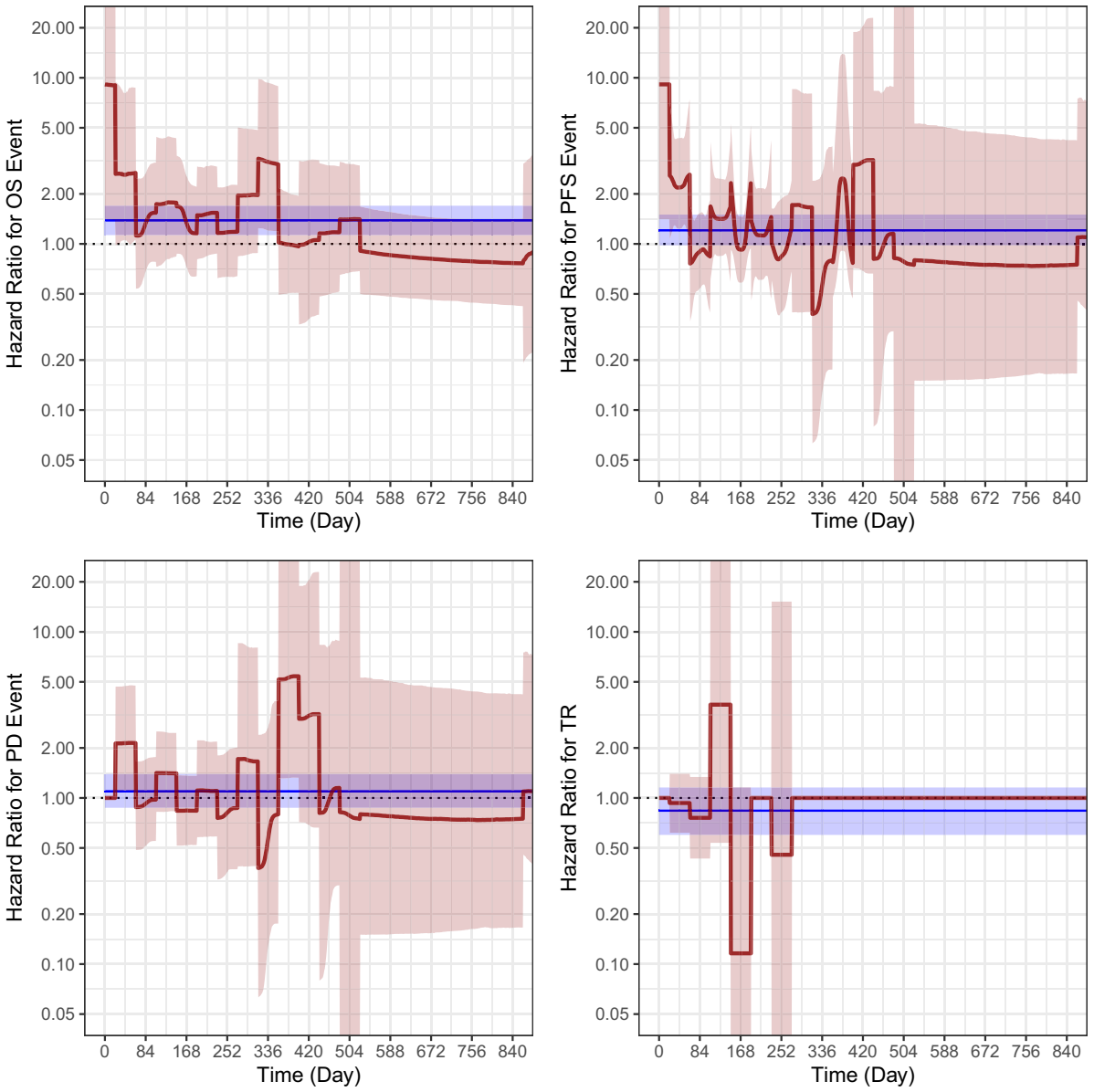

FIGURE 6 Estimated hazard ratios for OS, PFS, PD, and transition rate ratios for TR for subjects with high baseline ECOG scores versus the subjects with low baseline ECOG Scores. The estimated ratios and the corresponding 95% Bayesian credible bands by assuming proportional ratios over the entire time course are shown in blue, and the estimated ratios and the corresponding 95% credible intervals by assuming proportional ratios only within time segments are shown in red. Low ECOG Score: ECOG = 0; High ECOG Score: ECOG > 0; The limits of *y*-axes were set to 0.05 and 20 for better visualization of the temporal trends. ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; PD, progressive disease; OS, overall survival; TR, tumor response;

on the later events could be accessed. The parametric approach also enables clinical trial simulations to explore different clinical trial designs and the corresponding possible outcomes to inform oncology trial designs and interpretations. This parametric approach may provide a deeper understanding of causal elements for observed differences in treatment outcomes when comparing competing regimens. In addition, the covariate/treatment effect on hazards can be evaluated in a time-variant fashion. The estimated time-variant hazard ratios could serve as a diagnostic tool for confirming treatment effect and/or identifying meaningful covariates associated with disease prognosis. Whereas improvement of OS is the most clinically meaningful endpoint in oncology trials, the early surrogate, PFS, is more commonly used for drug approval decisions.[17] However, only one-fifth of cancer drug indications approved via the US Food and Drug Administration's accelerated approval pathway conducted the confirmatory trials using OS as an endpoint and demonstrated improvements in OS.[18] The multistate model could provide

additional information to support go and no-go decision early in oncology development by evaluating the correlations between PFS and OS and the treatment effects on hazards to all key events included in the model in addition to PFS and OS.

The model includes many parameters. Selection of initial values is essential to stabilize the model runs, reduce the runtime, and ensure reasonable model fits. Derivative-free optimization algorithm, such as genetic algorithm, was implemented to find good initial parameter values.[19] The script is provided in the supplementary materials. When evaluating a covariate effect on hazard over a specific time segment, events at different covariate levels are needed to provide information for estimating covariate effects. In the current model, the hazard ratio was fixed to 1 when events at different covariate levels were not available over the time segment. To prevent fixing the hazard ratio to 1, the model could incorporate time-variant covariate effects over longer consecutive time segments (e.g., early, middle, and late time periods in the trial) to ensure sufficient events at different covariate levels are observed over the time periods. The piecewise multistate model can also be implemented in NONMEM using the Laplace method for parameter estimation.[20] As NONMEM implements a gradient-dependent method, the execution time would be shorter, but it is slightly easier to encounter numerical issues compared to the Bayesian approach using Markov chain Monte Carlo (MCMC) sampling method in Stan. Although the MCMC based method requires longer run times to get sufficient samples to estimate posterior distributions, it is convenient to get posterior distributions for other derived quantities of interest when needed. To reduce run times, the closed form solutions for the integrals of piecewise functions were implemented in Stan.

The proposed multistate model has few assumptions. The time in the model is referring to the time post-randomization, so subjects with the same covariate level are assumed to have the same hazard functions and survival probabilities regardless of when they joined the trial. Before the time of occurrence of one of the competing events, the hazard functions and survival probabilities for the competing events are assumed to be independent, so the probability having no competing events at time t is the product of survival probabilities for all competing events at time t. The expected number of subjects at risk in different states are assumed to be continuous. Proportional hazards assumption is made for evaluating covariate effects.

With implementation of time-variant piece-wise hazard rate functions using ODEs in the analysis, longitudinal data, such as pharmacokinetics, biomarker, and tumor dynamics, can be included as forcing functions to drive the time-variant hazard rate functions. Their impacts on the hazard functions, for example, how tumor dynamics affect hazard of TR and progressive disease, can be quantitatively evaluated in a longitudinal manner. Moreover, under the ODEs framework, the model can integrate ODE-based models to better describe the mechanism behind the disease, such as exposure-response models linking drug exposure and tumor growth inhibition. This would enable identification of meaningful early efficacy markers and/or signals to inform decision making in the trial. Overall, the model could serve as a platform to integrate all available longitudinal data and other ODE-based models for oncology trials.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. C.-W.L. designed and performed the research and analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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